CIBA GEIGY AG *EP--33-518
01.02.80-CH-000836 (12.08.81) A61k-31/54 C07d-501/20

Crystalline cephalosporin antibiotic salt - is 7-2-(2-amino-4-thiazolyl) 2-methoxy imino acetamido-3-cephem-4-carboxylic acid pivaloyl:oxy:methyl ester hydrochloride

D/S: E(AT BE CH DE FR GB IT LI LU NL SE).

Crystalline 7β-[2-(2-amino-4-thiazolyl)-2-methoxyimino-acetamido] - 3-cephem-4-carboxylic acid pivaloyloxy-methyl ester hydrochloride (Ia) and hydrobromide (Ib) are new.

USE

(Ia) and (Ib) are useful as antibacterials.

ADVANTAGES

Unlike the pivaloyloxymethyl ester free base (which has the advantage of good gastrointestinal absorption but is difficult to obtain in pure form), (Ia) and (Ib) are readily obtainable in crystalline form and have improved stability. Thus, (Ia) and (Ib) are more suitable for conversion into pharmaceutical dosage form than the corresp. free base.

PREPARATION

Crystalline (Ia) and (Ib) are produced by treating 7β-[2-(2-amino-4-thiazolyl)-2-methoxyiminoacetamido] -3-cephem-4-carboxylic acid pivaloyloxymethyl ester (II) with HCl or HBr, and crystallizing the resulting salt. In a pref. procedure, (II) is dissolved in CH_2Cl_2 and treated with an equiv. amt. of HCl or HBr in CH_2Cl_2, CH_2Br_2 or Et_2O. The resulting soln. is concd. and/or treated with a non-polar solvent (e.g. Et_2O, pentane or hexane). Pptd. (Ia) or (Ib) can be crystallized or recrystallized from CH_2Cl_2.

EXAMPLE

A solution of (II) (4.97 g) in CH_2Cl_2 (50 ml) is treated at 0°C with 0.18 M HCl/CH_2Cl_2 (61 ml), stirred 10 mins., treated with Et_2O, and stirred 0.5 hr. at 0 °C. The precipitate is filtered off, washed with Et_2O, and dried in high vacuum at 30°C. The resulting crude (Ia) is dissolved in CH_2Cl_2 (50 ml) and the soln. is concd. and let stand overnight at 5°C. Product which crystallizes out is filtered off, washed with a small amount of CH_2Cl_2 and Et_2O and dried as before to give colourless (Ia), m.pt. 187-191°C.
(12pp280)
(G) ISR: EP---1125; EP---8343.